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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,947	05/29/2001	Alan John Kingsman	674523-2006.1	7750

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/867,947	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,16-18,20-22 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,16-18,20-22 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The specification has been amended, claims 1-10, 12-15, 19, 23-29 have been canceled, claims 11, 16-18, and 20-22 have been amended, and claim 30 has been added by the amendment dated January 30, 2002.

Applicant's statement with regard to a potential estoppel does not reflect the examiner's position on this issue.

Elected claims 11, 16-18, 20-22, and 30 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 16-18, 20-22, and 30 are rejected under 35 U.S.C. 112, first paragraph because the specification is only enabling for:

1/ A non-primate lentivirus based retroviral vector production system comprising nucleic acid sequence(s) encoding a non-primate lentivirus genome, gag, pol, and an envelople protein, wherein nucleic acid sequence(s) encoding a functional Tat are absent from the system, and wherein the genome, which comprises regulatory sequences of both the 5' LTR and 3' LTR, and a NOI coding sequence, wherein the genome lacks the *tat* gene but includes the leader sequences between the end of the 5'

LTR and the ATG of *gag;*

2/ The non-primate lentivirus based retroviral vector production system of 1/, wherein the non-primate lentiviral genome is obtained from EIAV);

3/ A non-primate lentiviral particle comprising a *gag-pol* coding sequence, and a non-primate lentiviral genome, which genome comprises regulatory sequences of both the 5' LTR and 3' LTR, packaging sequences comprising a nucleic acid coding for a functional *gag* protein, and a NOI coding sequence, wherein the genome lacks the *tat* gene but includes the leader sequences between the end of the 5' LTR and the ATG of *gag* (proposed amended claim for the pending claim 16);

4/ An isolated cell transfected or transduced with the non-primate lentiviral particle of 3/ (proposed amended claim for the pending claim 18);

5/ A delivery system comprising the non non-primate lentivirus based retroviral vector production system of 1/, and a pharmaceutically acceptable carrier.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative

skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As such and when given their broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species of retroviral particles based on a non-primate lentiviral genome, that do not necessarily contains a functional *gag* protein or packaging signal, which is essential to the making of replicated lentiviral particles, *e.g.,* see the specification, page 3, third full par.. However, the specification fails to provide an enabling disclosure for the making of such non-primate lentiviral particles other than the those found to be enabling as set forth the above enabling embodiments. In order to practice the claimed invention, a skilled artisan would turn to the specification and the general knowledge in the prior art for guidance. The state of the prior art indicates the following:

- Lentiviruses are a quasi-species composed of many variant genomes; thus, the sequence and biologic properties of a single provirus may not be definitive of the *in vivo* and *in vitro* macrobiology of the isolate (Garvey *et al.,* Virology, 175, 2, 391-409, 1990, page 407, column 1);
- Packaging of viral RNA into virions or viral particles depends on the presence of *cis* of encapsidation signals of 150 to 450 bps that have been localized to a region downstream of the 5' LTR in the vast majority of retroviruses (Gazit *et al.,* Virology 189, 344-349, 1992; p. 346, column 2);
- The presence of the 5' leader as well as the *gag* region in the defective CAEV (a non-primate lentivirus) genome would allow packaging of these defective

RNA molecules (Gazit *et al.,* p. 346, column 2);

- A minimum requirement of three vectors including a lentiviral packaging construct expressing functional *gag-pol* proteins is required for producing a recombinant lentiviral particle (Verma *et al.,* US Pat No. 6,013,516, Fig. 1, and column 4, first paragraph; and Kim *et al.,* J. of Virology, 1998, cited in IDS);
- Functional *gag* proteins (p55; or p24, p17, and p15) are essential for formation of the inner core of any retroviral particle including lentiviral particles (the prior art of record as cited in IDS);
- Domains of *gag* proteins including the carboxyl terminal part of the capsid proteins from HIV-1/2, SIV, and FIV are highly conserved and the carboxyl terminal region of the capsid proteins of lentiviruses and C-type retroviruses contains a domain that plays an essential role in the assembly of lentivrial particles (Poblozki *et al.* (Virology, Vol. 193, 2, 981-5, 1993, page 985, column 1); and
- A retroviral including lentiviral nucleotide sequence between the end of the 5' LTR and the *gag* initiation codon is essential for packaging a retroviral viral vector into retroviral particles (prior art cited in IDS).

However, the as-filed specification only provides sufficient guidance and/or evidence demonstration production of a non-primate lentiviral particle comprising a *gag-pol* coding sequence, and a non-primate lentiviral genome, which genome comprises regulatory sequences of both the 5' LTR and 3' LTR, packaging sequences comprising

a nucleic acid coding for a functional *gag* protein, and a NOI coding sequence, wherein the genome lacks the *tat* gene but includes the leader sequences between the end of the 5' LTR and the ATG of *gag* . Given the complexities of the nature of lentiviral proteins operated for formation of viral particles, the essential requirement functional *gag-pol* protein including nucleotides downstream from the 350 nucleotide of a *gag* coding sequence of lentiviruses known in the prior art, and the doubts expressed in the art of record as to the non-*gag* contained EIAV particles among all known non-primate lentiviruses, the skilled artisan would require an undue experimentation to reasonably extrapolate from the disclosure of the EIAV particles to the full scope of the claimed invention, particularly on the basis of applicant's disclosure. With respect to the claims drawn to a non-primate lentiviral production system, it is apparent from either the state of the prior art or the as-filed specification that not only the non-primate lentiviral vector of 1) is required for the system, but also that a *gag-pol* expressing construct together with regulatory/packaging sequences (env, for example), and a non-primate lentiviral packaging cell are required for the system. Thus, the proposed claim as set forth above would resolve the issue. In addition, applicant attempts to claim essentially just the non-primate lentivral vector of 1), for example, as a delivery system, however, it is apparent from the state of the prior art of record (Verma) that at least a pharmaceutically acceptable diluent or carrier is required for the delivery system.

In view of the reasons set forth above, it is not apparent how one skilled in the art, with out any undue experimentation, practices the full breadth of the claimed invention.

Applicant's response (page 13) has been considered by the examiner but is not found persuasive for the reasons of record.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

To the extent that claims 16-18, 20-22 are readable on a lentiviral and/or a non-primate lentiviral vector that contains no *tat* gene, which is employed in a three vector system which separately comprises a *gag-pol* expressing construct and/or a packaging construct that comprises nucleotide sequence between the splice donor site and the *gag* initiation codon of a *gag* coding sequence so as to produce retroviral particles, and that the claims are readable on a vector or particle obtained from the system, and/or cells transfected by the obtained vector or particle, the following rejections are applicable.

Claims 16-18, 20-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Olsen (US Pat No. 6,521,457 B2).

The claims embrace a EIAV vector produced by a three vector system, wherein the tat gene is not rendered non-functional, and where the EIAV vector is not claimed specifically in any structural form, the rejection over the Olsen remains applicable.

Olsen teaches a vector production system, EIAV particles, and a delivery system, each of which comprises an EIAV vector that contains at least one defect in at least one encoding an EIAV structural protein, an expression cassette having an NOI coding sequence (abstract). Figures 3 and 4 describe an exemplified EIAV vector that can be used in a delivery system comprising a pharmaceutically acceptable carrier, wherein the

vector comprises regulatory sequences of both the 5' LTR and 3' LTR, a packaging sequence comprising a nucleic acid coding for a functional *gag* protein. As such, a vector present in the system are lacking the *tat* gene. Column 6, lines 45-50 clearly discloses that the *tat* gene can be expressed *in trans* by a gag/.pol expression contruct which is used as one of the main constructs in a EIAV production system. Column 7 (second full par.) provides detailed description of an EIAV expression vector that is used as a NOI delivery vector, which vector at minimum only requires to contain cis-acting sequence elements required to support reverse transcription or replication, a functional *gag* coding sequence, and cloning sites for insertion of cDNAs encoding heterologous genes of interest.

Thus, Olsen anticipates the claims.

In view of applicant's statement set forth on page 15 of the response, the rejection of the remaining claims under 35 U.S.C. 102(e), as being anticipated by Kingsman (6,312,682, which has a distinct inventive entity, wherein Susan Kingsman constitutes as an antother), has been withdrawn by the examiner.

Applicant 's response with respect to the stated rejection under 35 USC 102, drawn to EIAV vector based system as claimed in claim 11, is found persuasive, and thus, overcomes the rejection of record.

However, applicant's response is not found persuasive for the presently pending claims, which embrace CAEV vector based system, wherein the Tat gene is dispensable.

Claims 16-18, 21, 22, and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Harmache (J. of Virology, p. 5445-5454, Vol. 69, 1995).

The claims embrace a CAEV vector based system as claimed in claim 30. Harmache teaches the same the throughout the reference (title, and abstract, and Table 2).

Thus, Harmache anticipates the claims.

Claims 16-18, 20-22, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harmach taken with Naldini *et al.* (US Pat No. 6,428,953), and Chang (US Pat No. 6,207,455).

To the extent that the claims embrace a non-primate lentiviral CAEV based particle, wherein the particle is employed as a delivery vector for delivering a NOI to a cell, the following rejection is applicable.

The teaching of Harmanche is applied here as indicated above. Harmache does not teach explicitely that the CAEV vector comprises a NOI and used as a delivery vector. However, Harmanched teaches that the *tat* gene is dispensible during the making or production of the CAEV particles.

However, at the time the invention was made, the concept of making lentiviral vectors as a delivery vector comprising a NOI in the absence of a functional *tat* gene is well-established in the prior art, as exemplified in Naldini and Chang. Both of Naldini (column 9, lines 55-56, for example) and Chang (column 28 through column 29) do

teach that as long as a strong heterologous LTR (CMV-IE-LTR) is employed to increase basal promoter activity, lentiviral replication such as HIV replication can be sustained without Tat.

As such, it would have been obvious for one of ordinary skill in the art to delete the *tat* gene from the CEAV system as described in Harmanche and employ the CEAV based particle as a delivery lentiviral vector comprising a NOI. One of ordinary skill in the art would have motivated to do so because such modifications are routine in the prior art, as disclosed in both Naldini and Chang, and because Chang teaches that a replication defective lentiral vector can be used a delivery vector comprising a NOI. One would have expected that CEAV can be made without the presence of a functional *tat* on the basis of the combined teachings provided by the references as a whole. The totality of the prior art of record, as exemplified, does teach generically that lentiviral particles including both primate and CEAV based particles can be made without the presence of a functional *tat*.

Thus, the claimed invention as a whole was *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11, 16-18, 20-22, and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 6,312,682 B1 in view of Olsen. Although the conflicting claims are not identical, they are not patentably distinct from each other because

Both set of claims embrace a non-primate lentiviral particle comprising a non-primate lentiviral genome, which comprises regulatory sequences of both the 5' LTR and 3' LTR, a packaging sequence comprising a nucleic acid coding for a functional *gag* protein, and a NOI coding sequence, wherein the genome lacks the *tat* gene. While the patent claims do not teach explicitly that the lentiviral particle includes but includes the leader sequences between the end of the 5' LTR and the ATG of *gag,* such is well-known in the prior art, as exemplified by Figure 1 of the patent and the disclosure of Olsen. Further, while the patent claims are silent about EIAV, such would constitute as an obvious variant of the patent claims, since the prior art as exemplified by Olsen teaches a vector production system, EIAV particles, and a delivery system, each of which comprises an EIAV vector that contains at least one defect in at least one encoding an EIAV structural protein, an expression cassette having an NOI coding sequence (abstract). Figures 3 and 4 of Olsen also describe an exemplified EIAV

vector that can be used in a delivery system comprising a pharmaceutically acceptable carrier, wherein the vector comprises regulatory sequences of both the 5' LTR and 3' LTR, a packaging sequence comprising a nucleic acid coding for a functional *gag* protein. As such, it would have been obvious for one of ordinary skill in the art to have applied the teaching of the patent claims to the making and use of any non-primate lentiviral particle such as EIAV. Thus, both sets of patent claims and examined claims are obvious variants of one another.

The examiner acknowledges that the previous ODP rejection has a typographical error with respect to the recitation of "6,521,457", since the patent claims do not have 62 claims. The above ODP rejection has corrected the typographical error.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(571-272-0731)**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson* may be reached at **571-272-0184.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN